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Reticular dysgenesis: report of two brothers

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SUMMARY

We describe two brothers with marked leucopenia, lymphopenia, no immunological response to infections (no Ig production, negative PHA response and very low number of T and B lymphocytes in peripheral blood) and hypocellular marrow. They died at 12 and 8 days of life with infection (*E. coli* and Klebsiella, respectively).

INTRODUCTION

Reticular dysgenesis is a very rare and severe form of immunodeficiency (Cooper *et al.*, 1973; Waldmann & Broder, 1978) characterised by congenital leucopenia, lymphopenia, absent Ig production, lymphoid hypoplasia and thymic agenesia, which is manifested with severe progressive neonatal infections. We describe two affected brothers.

CASE REPORTS

The patients were the first and second children of young, healthy and unrelated parents. There was no relevant family history. The pregnancies were normal, with no history of illness, intoxication or irradiation. Relevant haematological and immunological data from the parents are shown in Table 1.

TABLE 1. Haematological and immunological data of the parents

	Blood group	Histocompatibility testing	Erythrocytic adenosine deaminase*
Mother	A_1 Rh (−)	HLA-Aw 33·24 (9) B 7·14 (w6)	0·701 μ/g Hb
Father	0 Rh (−)	HLA-A 3·11 B 8·44 (12 w6, w4) Cw5	0·814 μ/g Hb

* Method of Beutler (1975). Normal values (from control adult population): 0·87–1·29 μ/g Hb.

Case 1

A 10 day-old male, body weight 2·3 kg, developed omphalitis at nine days of age. The umbilical stump was infected with phlebitis of the abdominal wall, necrotic lesions in the perineal area and a small abscess behind the ear. Haematological and immunological data are shown in Table 2. Umbilical exudate, throat, gastric contents and urine cultures grew *E. coli* colonies. CSF culture was sterile. Chest X-ray: no thymic shadow.

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He was treated with intravenous fluid and antibiotics (ampicillin and gentamicin). Necrotic lesions developed very rapidly, spreading on the abdomen, and perianal area; he deteriorated and died 44 hr after admission.

TABLE 2. Haematological and immunological data of the patients

	1st Patient		2nd Patient	
Age (days)	10	1	3	8
PVC (%)	42	54	40	—
Leucocytes/mm^3	1100	3300	750	500
lymphocytes (%)	22	76	74	
neutrophils (%)	70	24	6	
monocytes (%)	8		20	
Platelets/mm^3	—	250,000	250,000	25,000
Bone marrow smear	—		Very hypocellular (only megakaryocytes)	
Total proteins g/l	43	54	—	—
IgG i.u./ml	14	110	—	90
IgM i.u./ml	16	19		12
IgA i.u./ml	4·1	4·7		4
C_3 mg/ml	—	100	—	—
C_4 mg/ml		49		
Lymphocyte response to PHA*	—	1631/1701	1005/2440	(Control: 1860/84,738)
E-rosettes (%)†	—	3		(Control: 54)
EAC-rosettes (%)	—	2		(Control: 20)
Surface Ig (%)‡	—	0		(Control: 10)

* Thymidine uptake. Whole blood culture: c.p.m. unstimulated culture/c.p.m. stimulated culture. (Espanol, Todd & Soothill, 1974).

† Methods of lymphocyte separation, E and EAC rosette formation of Fleisher *et al.* (1975) and Gupta & Good (1977).

‡ Immunofluorescence method for surface Ig of Santana, Wedderburn & Turk (1973) using polyvalent anti-immunoglobulin antiserum (Behring Institut).

Case 2

This newborn male was transferred from another hospital because of his brother's immunodeficiency. Body weight 2·4 kg. Physical examination was normal. Chest X-ray: absence of the thymic shadow. Nose, throat, urine and faeces cultures were negative. The number of leucocytes was low and diminished further without clinical evidence of disease while immunological response was also absent, (Table 2). He was nursed with barrier precautions, but he developed diarrhoea on the third day of life, and Klebsiella grew in cultures of urine, faeces and throat; antibiotic therapy was began. Despite treatment he deteriorated with abdominal swelling, watery stools and hypertonia. Cerebrospinal fluid contained 2·5 g/l of protein with 190 red cells/mm^3 but no white cells; there were many colonies of Klebsiella. Nasogastric feeding was stopped because of haemorrhagic vomiting. Jaundice appeared on the fifth day of life (bilirubin: 5·2 mg). He died eight days after admission.

AUTOPSY FINDINGS

Thymus. In both cases the thymus was very small (1 g). Histological examination showed a small number of lobules separated by relatively thick connective tissue. The cells making up the lobules were almost entirely reticular cells. Cortex-medulla differentiation was absent. The number of lymphocytes was very low and only present in small foci of the medullary area. Small acidophilic masses, like primitive Hassall's bodies, were present (Fig. 1a, b).

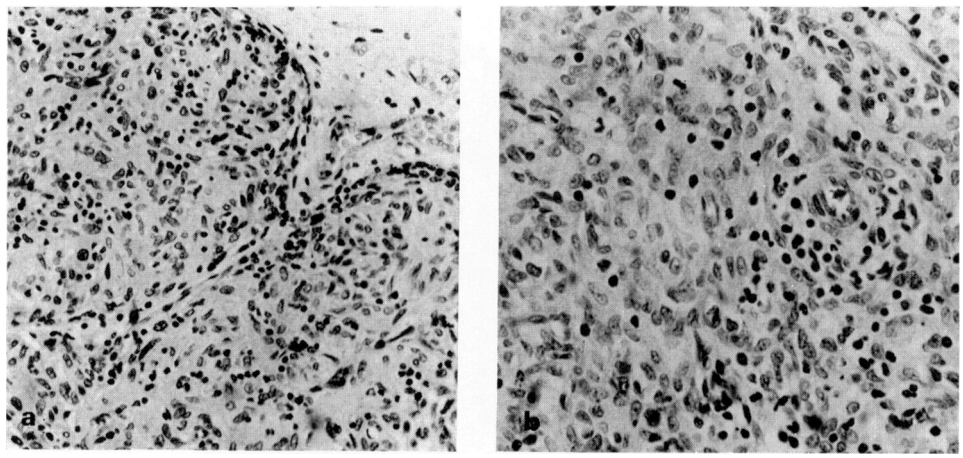

FIG. 1a, b. Thymus from the first and second case. (H & E, ×210 and 330.)

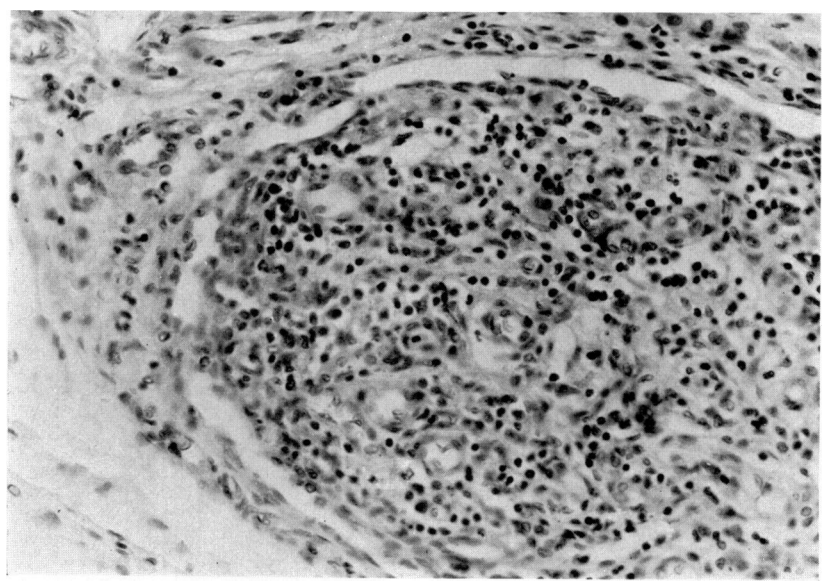

FIG. 2. Lymph node. (H & E, ×300.)

Lymph nodes. Macroscopically the nodes were very small. Although the sinusoidal architecture was recognizable, they were almost devoid of lymphocytes and no lymphoid follicles were seen. A few histiocytes were present in the sinuses (Fig. 2).

Gut. In the gastro-intestinal tract reticular-like cells were seen, with marked depletion of lymphocytes. No plasma cells were seen (Fig. 3).

Spleen. Normal size. The section was devoid of lymphoid tissue, though there was a little extra-medullary haemopoiesis indicated by the presence of megakaryocytes; the usual periarterial cuffing was absent. There was some increase in interstitial connective tissue and phagocytic cells were seen to line some sinusoids. In the second case, haemosiderin and sinusoid dilatation were seen (Fig. 4a, b).

Bone marrow. Very similar in both cases: markedly hypocellular with much of the marrow space occupied by erythrocytes. Megakaryocytes were present in normal or slightly increased numbers.

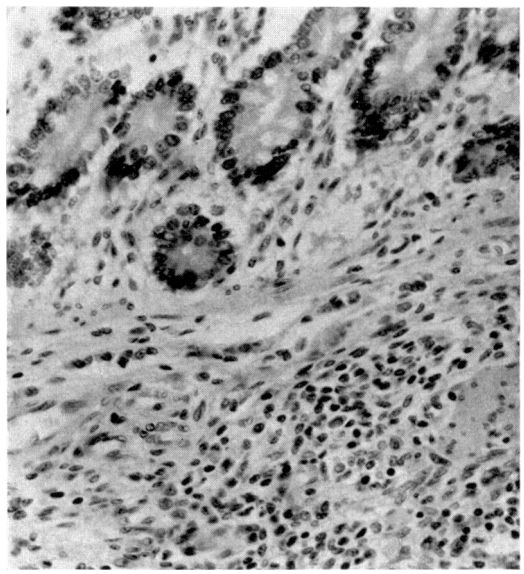

FIG. 3. Gut. (H & E, × 300.)

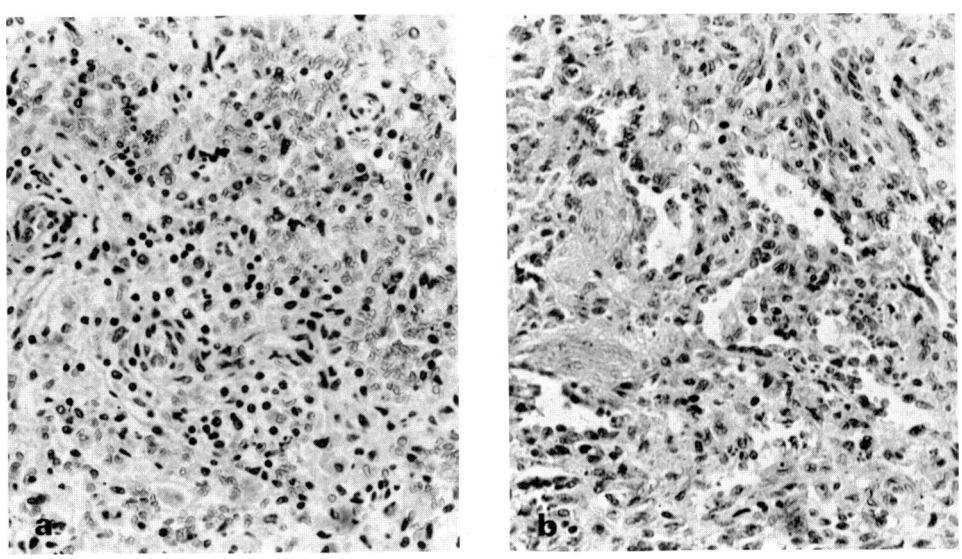

FIG. 4a, b. Spleen from the first and second case. (H & E, × 240.)

Erythroid cells were normally grouped and present in normal numbers. Myeloid cells were greatly reduced in number. The marrow and surrounding soft tissues appeared normal (Fig. 5).

Umbilicus. In the first case, there was a marked inflammatory reaction with oedema, fibrin deposits and many bacteria, but no polymorphonuclear cells.

Lungs. Most of the alveoli contained proteinaceous material, numerous bacteria, but no polymorphonuclear cells.

Oesophagus. In the second case, there was an extensive ulceration of the inferior third, with many bacteria but no cellular reaction.

Central nervous system. The second case also revealed congested meninges and swollen and softened cerebral tissue.

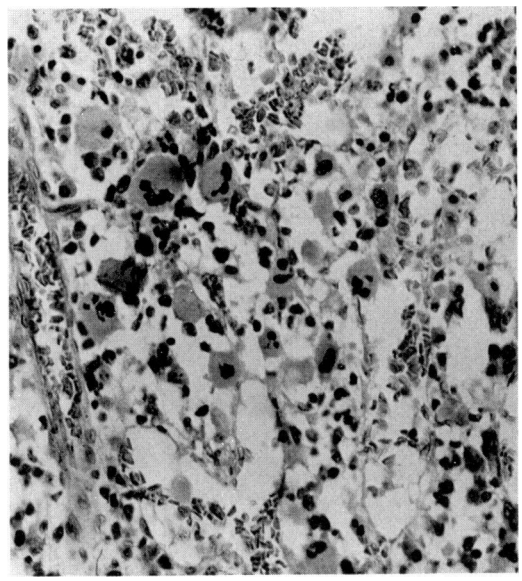

FIG. 5. Bone-marrow. (H & E, × 300.)

DISCUSSION

Reticular dysgenesis was first described by De Vaal (De Vaal, 1959) in male twins with aleucocytosis at birth, who died in the first eight days of life. Other cases have been reported (Alonso, Dew & Starke, 1972; Gitlin, Vawter & Craig, 1964; Haas *et al.*, 1977; Ownby *et al.*, 1976). All, except two, were males, and the life span ranged between three and eighty-four days. The number of leucocytes was also variable and in direct relationship with survival time. Most of them had a normal number of erythrocytes during the first days of life, but they decreased later. All had a normal number of platelets. The pathology findings were similar in all of them, and it was suggested that the disease was a stem cell defect.

It is now generally accapted that all blood cells come from a single precursor (Rosse & Press, 1978). The influence of other organs are needed for the complete maturation of some cells (thymus maturation for T lymphocytes), but the majority leave the bone marrow prepared to perform their function. Failure of differentiation and proliferation of the primordial stem cell would lead to different diseases, depending upon the timing of the development failure: the defect may involve only lymphocyte production (severe combined immunodeficiency) or both granulocyte and lymphocyte production. The involvement of the erythroid cell line is not a regular feature of the reticular dysgenesis and this suggests the stage of the defect. The presence of some lymphocytes and granulocytes on the first day of life, in case 2, could be related to the passive transfer of a maturation factor from the mother.

The family history is compatible with an autosomal inheritance, or X-linked inheritance as suggested in other reports, and, if so, presumably the primary gene product concerned is an enzyme or structural protein necessary for this differentiation. Severe combined immunodeficiency may be associated with adenosine deaminase deficiency (Meuwissen, Pollara & Pickering, 1975) but this has not been studied in reticular dysgenesis. It is unfortunate that we were not able to study this in the patients, but it is interesting that both parents, especially the mother, have low values.

So far, the disease has been consistently fatal, and the only hope at present would be isolation and tissue matched sibling bone marrow graft (Biggar, Park & Good, 1973) but no such donor was available in our family.

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